

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

FILE 86 69158/001	14 AUG 2000
RECEIVED	R

Date of mailing  
(day/month/year)

11 08 2000

Applicant's or agent's file reference  
86.89.69158/001

ANSWER

R

IMPORTANT NOTIFICATION

International application No.  
PCT/GB99/01388

International filing date (day/month/year)  
05/05/1999

Priority date (day/month/year)  
05/05/1998

Applicant  
WA PHARM AB et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

**4. REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/   European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer  Sinanovic, E Tel. +31 70 340-2672
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# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 86.89.69158/001	FOR FURTHER ACTION <span style="float: right;">See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)</span>	
International application No. PCT/GB99/01388	International filing date (day/month/year) 05/05/1999	Priority date (day/month/year) 05/05/1998
International Patent Classification (IPC) or national classification and IPC C07K14/685		
<p><b>Applicant</b> WA PHARM AB et al.<sup>§</sup></p> <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 3 sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the report</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV <input type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI <input type="checkbox"/> Certain documents cited</li> <li>VII <input type="checkbox"/> Certain defects in the international application</li> <li>VIII <input checked="" type="checkbox"/> Certain observations on the international application</li> </ul>		

Date of submission of the demand 04/11/1999	Date of completion of this report 11.08.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Groenendijk, M Telephone No. +31 70 340 3715



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01388

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-62 as originally filed

**Claims, No.:**

1 (part), 4 (part), as originally filed  
5, 13-64

1 (part), 2, 3, 4 (part), as received on 16/06/2000 with letter of 16/06/2000  
6-12

**Drawings, sheets:**

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

the description, pages:  
 the claims, Nos.:  
 the drawings, sheets:

3.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01388

- the entire international application.
- claims Nos. 30-64 with respect to industrial applicability.

because:

- the said international application, or the said claims Nos. 30-64 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N) - Yes: Claims 1-64  
No: Claims

Inventive step (IS) Yes: Claims 9  
No: Claims 1-8,10-64

Industrial applicability (IA) Yes: Claims 1-64(see the Separate Sheet)  
No: Claims

**2. Citations and explanations**

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01388

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01388

**Re Item I**

Basis of the opinion

The corrections made in the claims 2,11 and 12 are considered to be acceptable under Rule 91 PCT.

**Re Item III**

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 30-64 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: J.Biol.Chem., Vol.272, 1997, 27943-27948

**I.NOVELTY**

In view of the available prior art the claims 1-64 are considered to be novel under Art.33(2) PCT.

**II.INVENTIVE STEP**

- 1)The closest prior art is considered to be D1 disclosing melanocortin receptor 1 (MCR1) specific peptides obtained by phage display selection having a sequence which is very similar to those disclosed in the claims 1 and 6 (see Table 3) and which compounds have been demonstrated to exhibit a MCR1 modulated biological activity.
- 2)The compounds of the present application differ from said prior art compounds essentially therein that the C-terminal three amino acid residues are identical to the

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01388

corresponding amino acid residues of alpha-MSH. Furthermore some mainly conserved substitutions are allowed in the N-terminal part of the compounds compared to the prior art compounds and the facultative application of usual N-alkylation or backbone modifications to improve the enzymatic resistance have been claimed. According to the experimental data of the examples 2 and 3 at least some of the compounds appear to have an improved affinity to MCR1 and a higher cAMP formation, be it somewhat at the expense of the selectivity for MCR1.

3)The problem to be solved may therefore be considered to be the provision of MCR1 specific peptides having an improved biological activity.

4)It is true that in D1 it was already indicated that the amino acid in position 12 of  $\alpha$ -MSH (Pro) is important for the MCR1 binding (see page 27947, column 2). An expert would therefore expect that substitution of Cys by Pro in the sequence MS-04 in table III of D1 would raise the MCR1 binding properties and also solve the instability of the compound due to the Cys sidechain.

However the examiner is of the opinion that the strong increase in binding to MCR1 and in the agonistic activity, while maintaining the high specificity for MCR1, could not be expected on the basis of the teaching of D1. Consequently compounds having said combination of advantageous properties are considered to involve an inventive step under Art.33(3) PCT.

5)At present said advantageous properties have only been demonstrated for the compound MS-05 and to a lesser extent for the compound MS-09. Therefore claim 9 is considered to fulfil the requirements of Art.33(3) PCT.

However from the experimental data of said compounds it appears that only minor structural changes already result in major differences in activity and specificity. The examiner thereof has serious doubts whether all of the novel compounds claimed actually show said advantageous properties and therefore solve the problem posed.

Therefore in order to acknowledge an inventive step under Art.33(3) PCT for the claims 1-8 and 10 and also (having regard to the general prior art concerning the biological activities regulated by MCR1, e.g., see the description on page 2 to page 4) the related claims 11-64, it should be made plausible by additional experimental data that the compounds comprised by that claims actually solve the problem posed.

In this respect it is noted that the mere application of N-alkylation or backbone modification in order to improve the enzymatic stability (claims 3 and 7) is not considered to contribute to the presence of an inventive step.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01388

For the assessment of the present claims 30-64 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VIII**

Certain observations on the international application

The claims 1,6,11 and 12 comprise expressions like "(substituted) (hetero)alkyl", "(substituted) (hetero)aryl" and "amino acid analogue", which expressions are open-ended, rendering the scope of the claims unclear under Art.6 PCT.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/01388

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 31-64

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 31-64 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2.  Claims Nos.:

because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3.  Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01388

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 C07K14/685 C12N15/16 A61K38/34

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SZARDNINGS E.A.: "Phage display selection on whole cells yields a peptide specific for melanocortin receptor 1"  <i>JOURNAL OF BIOLOGICAL CHEMISTRY</i>,    vol. 272, no. 44,    31 October 1997 (1997-10-31), pages    27943-27948, XP002113068    MD US    cited in the application    the whole document</p> <p>-----</p>	1-64

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

24 August 1999

Date of mailing of the international search report

03/09/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
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 Fax: (+31-70) 340-3016

Authorized officer

Groenendijk, M

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PATENT COOPERATION TREATY

PCT

REC'D 14 AUG 2000

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 86.89.69158/001	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB99/01388	International filing date (day/month/year) 05/05/1999	Priority date (day/month/year) 05/05/1998	
International Patent Classification (IPC) or national classification and IPC C07K14/685			
Applicant WA PHARM AB et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 3 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the report</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV <input type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI <input type="checkbox"/> Certain documents cited</li> <li>VII <input type="checkbox"/> Certain defects in the international application</li> <li>VIII <input checked="" type="checkbox"/> Certain observations on the international application</li> </ul>			

Date of submission of the demand 04/11/1999	Date of completion of this report 11.08.2000
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Groenendijk, M Telephone No. +31 70 340 3715



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01388

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-62 as originally filed

**Claims, No.:**

1 (part),4 (part), as originally filed  
5,13-64

1 (part),2,3,4 (part), as received on 16/06/2000 with letter of 16/06/2000  
6-12

**Drawings, sheets:**

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

the description, pages:  
 the claims, Nos.:  
 the drawings, sheets:

3.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01388

- the entire international application.
- claims Nos. 30-64 with respect to industrial applicability.

because:

- the said international application, or the said claims Nos. 30-64 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims 1-64
	No:	Claims
Inventive step (IS)	Yes:	Claims 9
	No:	Claims 1-8,10-64
Industrial applicability (IA)	Yes:	Claims 1-64(see the Separate Sheet)
	No:	Claims

**2. Citations and explanations**

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01388

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01388

**Re Item I**

**Basis of the opinion**

The corrections made in the claims 2,11 and 12 are considered to be acceptable under Rule 91 PCT.

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 30-64 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following document:

D1: J.Biol.Chem., Vol.272, 1997, 27943-27948

**I.NOVELTY**

In view of the available prior art the claims 1-64 are considered to be novel under Art.33(2) PCT.

**II.INVENTIVE STEP**

- 1)The closest prior art is considered to be D1 disclosing melanocortin receptor 1 (MCR1) specific peptides obtained by phage display selection having a sequence which is very similar to those disclosed in the claims 1 and 6 (see Table 3) and which compounds have been demonstrated to exhibit a MCR1 modulated biological activity.
- 2)The compounds of the present application differ from said prior art compounds essentially therein that the C-terminal three amino acid residues are identical to the

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01388

corresponding amino acid residues of alpha-MSH. Furthermore some mainly conserved substitutions are allowed in the N-terminal part of the compounds compared to the prior art compounds and the facultative application of usual N-alkylation or backbone modifications to improve the enzymatic resistance have been claimed. According to the experimental data of the examples 2 and 3 at least some of the compounds appear to have an improved affinity to MCR1 and a higher cAMP formation, be it somewhat at the expense of the selectivity for MCR1.

3) The problem to be solved may therefore be considered to be the provision of MCR1 specific peptides having an improved biological activity.

4) It is true that in D1 it was already indicated that the amino acid in position 12 of  $\alpha$ -MSH (Pro) is important for the MCR1 binding (see page 27947, column 2). An expert would therefore expect that substitution of Cys by Pro in the sequence MS-04 in table III of D1 would raise the MCR1 binding properties and also solve the instability of the compound due to the Cys sidechain.

However the examiner is of the opinion that the strong increase in binding to MCR1 and in the agonistic activity, while maintaining the high specificity for MCR1, could not be expected on the basis of the teaching of D1. Consequently compounds having said combination of advantageous properties are considered to involve an inventive step under Art.33(3) PCT.

5) At present said advantageous properties have only been demonstrated for the compound MS-05 and to a lesser extent for the compound MS-09. Therefore claim 9 is considered to fulfil the requirements of Art.33(3) PCT.

However from the experimental data of said compounds it appears that only minor structural changes already result in major differences in activity and specificity. The examiner thereof has serious doubts whether all of the novel compounds claimed actually show said advantageous properties and therefore solve the problem posed. Therefore in order to acknowledge an inventive step under Art.33(3) PCT for the claims 1-8 and 10 and also (having regard to the general prior art concerning the biological activities regulated by MCR1, e.g., see the description on page 2 to page 4) the related claims 11-64, it should be made plausible by additional experimental data that the compounds comprised by that claims actually solve the problem posed.

In this respect it is noted that the mere application of N-alkylation or backbone modification in order to improve the enzymatic stability (claims 3 and 7) is not considered to contribute to the presence of an inventive step.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01388

For the assessment of the present claims 30-64 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VIII**

Certain observations on the international application

The claims 1,6,11 and 12 comprise expressions like "(substituted) (hetero)alkyl", "(substituted) (hetero)aryl" and "amino acid analogue", which expressions are open-ended, rendering the scope of the claims unclear under Art.6 PCT.

-CH<sub>2</sub>X, where X is H, alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, alkenyl, substituted alkenyl, heteroalkenyl, substituted heteroalkenyl, alkynyl, substituted alkynyl, heteroalkynyl, substituted heteroalkynyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, cycloalkenyl, substituted cycloalkenyl, cycloheteroalkenyl, substituted cycloheteroalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, functional group,

and wherein NT is selected from H, hydroxyl, alkyl, aminoacid, aminoacid analogue, polypeptide and functional group, and CT is selected from hydrogen, hydroxyl, alkyl, aminoacid, aminoacid analogue, polypeptide and functional group, and wherein each asymmetric center (\*) is in R or S configuration;

the compound optionally possessing one or several of the following properties:

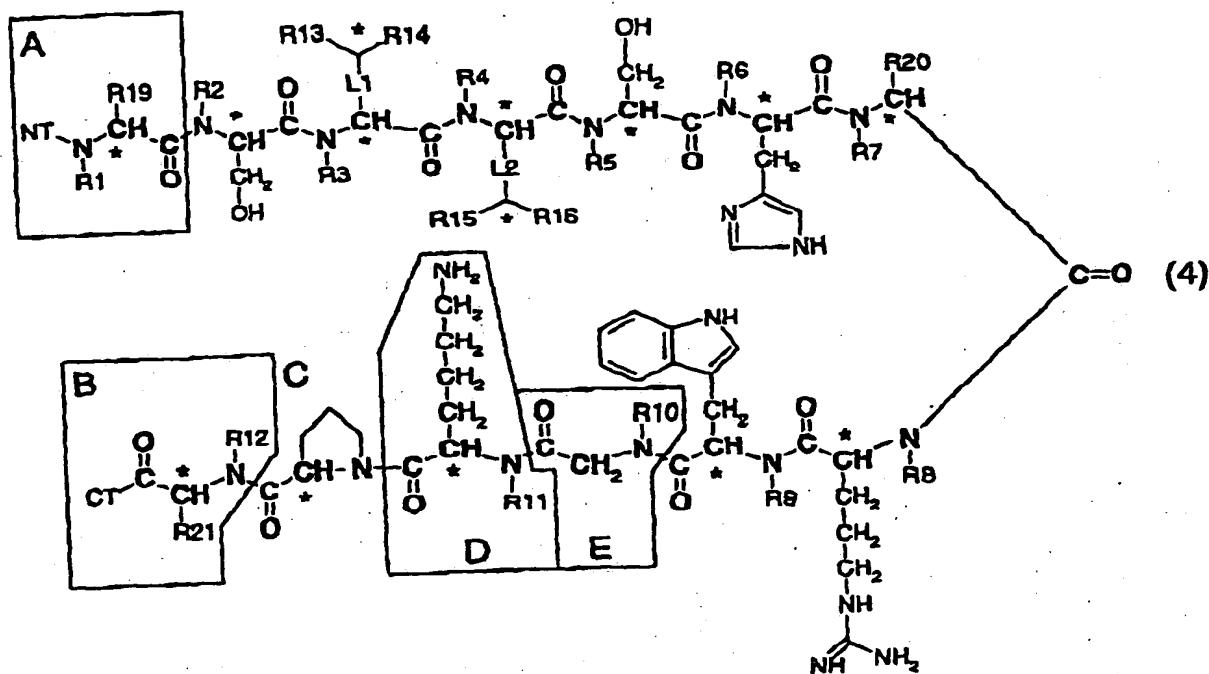
- 15 a) showing high affinity for MC1 receptors, and/or
- b) showing high selectivity for MC1 receptors, and/or
- c) showing high capacity to stimulate the second messenger cAMP, and/or,
- 20 d) being an effective inhibitor of NO production.

2. The compound of claim 1, wherein R20 is -CH<sub>2</sub>X, wherein X is phenyl.

- 25 3. The compound of claim 1 or 2, wherein one or several of the nitrogens of the peptide backbone have been exchanged for carbon substituted with hydrogen, and/or wherein one or several of the oxygens of the carbonyl groups of the peptide backbone has been exchanged for two hydrogens.
- 30 4. The compound of any one of claims 1 to 3, having the stereomeric conformation given in the general formula (2):

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6. A compound of the general formula (4):



20 wherein R1 to R16, R19 to R21, NT and CT are as defined in claim 1,

wherein moiety A is optionally exchanged for hydrogen, hydroxyl, alkyl, aminoacid, aminoacid analogue, polypeptide, or functional group,

25 wherein moiety B is optionally exchanged for hydrogen, hydroxyl, alkyl, aminoacid, aminoacid analogue, polypeptide, or functional group,

wherein optionally moiety D is exchanged for aminoacid or aminoacid analogue,

30 and wherein optionally moiety E is exchanged for aminoacid or aminoacid analogue.

7. A compound according to any one of claims 1-4 or 6, wherein one or several of R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11 and R12 are selected to be methyl, whereas the rest is selected to be hydrogen, the selections being made so as to prevent or 35 decelerate breakdown by proteases and/or peptidases.

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8. A compound according to any one of claims 1-4 or 6, wherein I is less than 6, preferably less than 5, more preferred less than 4 and preferably less than 2, and most preferred none of the R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11 and R12 are methyl.

5

9. A compound comprising the sequence Ser-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (SEQ ID NO:1), wherein the amino-acids are all L-amino-acids.

10. A compound comprising one of the followings sequences:

10

Ser-Ser-Ile-Ile-Ser-His-dPhe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (MS-09) (SEQ ID NO:2)

Tyr-Ser-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (MS-30) (SEQ ID NO:3)

Tyr-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (MS-31) (SEQ ID NO:4)

Ser-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Tyr-NH<sub>2</sub> (MS-32) (SEQ ID NO:5)

15

Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (MS-33) (SEQ ID NO:6)

Thr-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (MS-34) (SEQ ID NO:7)

Ser-Thr-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (MS-35) (SEQ ID NO:8)

Ser-Ser-Val-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (MS-36) (SEQ ID NO:9)

Ser-Ser-Ile-Val-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (MS-37) (SEQ ID NO:10)

20

Ac-Ser-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (MS-38) (SEQ ID NO:11)

dSer-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (MS-39) (SEQ ID NO:12)

NMeSer-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (MS-40) (SEQ ID NO:13)

Ser-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-NMeVal-NH<sub>2</sub> (MS-41) (SEQ ID NO:14)

Ser-Ser-Ile-Ile-Ser-His-NMedPhe-Arg-Trp-Gly-Lys-Pro-Val-NH<sub>2</sub> (MS-42) (SEQ ID NO:15)

25

11. A compound according to any one of claims 1-4 or 6-8, in which R20 is -CH<sub>2</sub>X, wherein X is aryl, substituted aryl, heteroaryl, substituted heteroaryl, phenyl or substituted phenyl, or a compound according to any one of claims 5, 9 or 10, wherein the compound is capable of activating MC1-receptors.

30

12. A compound according to any one of claims 1-4 or 6-8, in which R20 is -CH<sub>2</sub>X, wherein X is aryl, substituted aryl, heteroaryl, substituted heteroaryl, naphthalene, or substituted naphthalene, or a compound according to any one of claims 5, 9 or 10, wherein the compound is capable of blocking MC1-receptors.

35

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**ATENT COOPERATION TREATY**  
**PCT**

**INTERNATIONAL SEARCH REPORT**

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference  86.89.69158/001	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No.  PCT/GB 99/ 01388	International filing date (day/month/year)  05/05/1999	(Earliest) Priority Date (day/month/year)  05/05/1998
Applicant  WA PHARM AB et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

**2.  Certain claims were found unsearchable (See Box I).**

**3.  Unity of invention is lacking (see Box II).**

**4. With regard to the title,**

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

**5. With regard to the abstract,**

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. The figure of the drawings to be published with the abstract is Figure No.**

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/01388

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 31-64

because they relate to subject matter not required to be searched by this Authority, namely:

**Remark:** Although claims 31-64 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2.  Claims Nos.:

because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3.  Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 99/01388A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07K14/685 C12N15/16 A61K38/34

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SZARDNINGS E.A.: "Phage display selection on whole cells yields a peptide specific for melanocortin receptor 1" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 44, 31 October 1997 (1997-10-31), pages 27943-27948, XP002113068 MD US cited in the application the whole document</p> <p>-----</p>	1-64

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## ° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

24 August 1999

03/09/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Groenendijk, M

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 31 October 2000 (31.10.00)
Applicant's or agent's file reference 86.89.69158/001
International application No. PCT/GB99/01388

From the INTERNATIONAL BUREAU

To:

PETT, Christopher, Phineas  
Frank B. Dehn & Co.  
179 Queen Victoria Street  
London EC4 4EL  
ROYAUME-UNI

1. The following indications appeared on record concerning:				
<input checked="" type="checkbox"/> the applicant <input type="checkbox"/> the inventor <input type="checkbox"/> the agent <input type="checkbox"/> the common representative				
Name and Address WA PHARM AB c/o Melacure Therapeutics AB Uppsala Science Park S-751 83 Uppsala Sweden	State of Nationality		State of Residence	
	SE		SE	
	Telephone No.			
	Facsimile No.			
	Teleprinter No.			
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:				
<input type="checkbox"/> the person <input type="checkbox"/> the name <input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence				
Name and Address WA PHARM AB c/o Melacure Therapeutics AB Ulleråkersvägen 38 S-756 43 Uppsala Sweden	State of Nationality		State of Residence	
	SE		SE	
	Telephone No.			
	Facsimile No.			
	Teleprinter No.			
3. Further observations, if necessary:				
4. A copy of this notification has been sent to:				
<input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input type="checkbox"/> the International Preliminary Examining Authority		<input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other:		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Peggy Steunenberg  Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 31 October 2000 (31.10.00)
Applicant's or agent's file reference 86.89.69158/001
International application No. PCT/GB99/01388

From the INTERNATIONAL BUREAU

To:

PETT, Christopher, Phineas  
Frank B. Dehn & Co.  
179 Queen Victoria Street  
London EC4 4EL  
ROYAUME-UNI

## IMPORTANT NOTIFICATION

International filing date (day/month/year) 05 May 1999 (05.05.99)
--

## 1. The following indications appeared on record concerning:

the applicant  the inventor  the agent  the common representative

Name and Address MUCENIECE, Ruta Sernanders väg 3 S-752 61 Uppsala Sweden Sweden.	State of Nationality LV	State of Residence SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person  the name  the address  the nationality  the residence

Name and Address MUCENIECE, Ruta Sernanders väg 3/333 S-752 61 Uppsala Sweden Sweden	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other:
--	---

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Peggy Steunenberg  Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION  
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C.20231  
 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 24 November 1999 (24.11.99)	Applicant's or agent's file reference 86.89.69158/001
International application No. PCT/GB99/01388	Priority date (day/month/year) 05 May 1998 (05.05.98)
International filing date (day/month/year) 05 May 1999 (05.05.99)	
Applicant SZARDENINGS, Michael et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

04 November 1999 (04.11.99)

in a notice effecting later election filed with the International Bureau on:

\_\_\_\_\_

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer S. Mafia
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38